REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16-18, 22-26, 30-34 36, and 39-55, the only claims pending and currently under examination in this application following entry of the above requested amendments.

Claims 16, 24, and 30 have been amended to exactly match the wording of the specification at page 20, lines 26-27, regarding the affinity of the targeting molety for the intracellular biodistribution modulating protein. Claims 17 and 18 have been amended to correct antecedent basis in the claims with respect to "host". No new matter has been introduced to the application by the above amendments. As such, the Examiner is respectfully requested to enter the above amendments.

Allowable Subject Matter

The Applicants acknowledge with gratitude the Examiner's indication that Claims 39-56 are directed to allowable subject matter.

Objection to the Claims

Claim 24 has been objected to be the Examiner because the term "targeting moieties" in line 5 does not correspond to "a targeting moiety" in line 4. In view of the amendment to the Claim 24, this objection may be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph – Enablement

The Office Action maintains the rejection of Claims 16-18, 22-26, 30-34 and 36 under 35 U.S.C. § 112, 1st ¶ for an asserted lack of enablement. This rejection is respectfully traversed.

In particular, the Office Action states that the specification is enabling for a method for directing the biodistribution of a drug that binds to a protein target by administering to a mammalian host a bifunctional molecule comprising a targeting moiety and a drug moiety, wherein the targeting moiety is a peptidyl-prolyl isomerase ligand for FKBP or cyclophilin selected from the group consisting of FK506, rapamycin

and cyclosporine. As Applicants understand it, the rejection is based on the assertion that the specification does not provide enablement for a method:

(A) wherein the targeting moiety of the bifunctional molecule is any molecule that binds to all intracellular biodistribution modulating proteins (e.g., Office Action, paragraph bridging pages 3 and 4);

(B) wherein the drug moiety of the bifunctional molecule is any "small molecule" (e.g., Office Action, page 4, first paragraph), and

(C) wherein the drug moiety of the bifunctional molecule is any "drug derivative" (e.g., Office Action, page 4, first paragraph)/

These aspects of the rejection are addressed below.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

Disclosure of the Present Application

The Applicants maintain that the present application provides sufficient disclosure to enable the invention to the full scope of the pending claims. As previously argued in the amendment filed June 3, 2004 in response to the Office Action dated December 3, 2003, the present specification clearly provides extensive description of the bifunctional molecules employed in the subject methods beginning at page 4 of the specification. This includes a generic description of these molecules, a detailed description of these molecules in terms of formulas, an extensive description of each of the component parts of the molecules, e.g., drug moleties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23).

In addition, a detailed description of how to make the targeted bifunctional molecules is provided at pages 24 to 28 of the specification, where specific guidance is provided on how to make the compounds. Three representative methods of making the

[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

compounds are described. Furthermore, page 26 provides even more detail regarding bifunctional molecules of the invention that include a peptidyl-prolyl isomerase-targeting molety.

Guidance on how to screen candidate bifunctional molecules for suitability of use in the claimed methods is provided on page 25. Finally, page 29 of the specification provides an extensive description on how to use the bifunctional molecules in various applications, including dosages and administration routes, types of hosts, types of conditions, etc.

Therefore, the Applicants maintain that the methods disclosed in the present specification in conjunction with the knowledge available in the art at the time the present application was filed, would enable one of ordinary skill in the art to practice the invention to the full scope of the pending claims.

In re Wands Factors

In addition, the Applicants emphasize that under In re Wands, Claims 6-18, 22-26, 30-34 and 36 are fully enabled.

According to *In re Wands*, a determination of enablement, requires consideration of eight factors, including: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims. [2] Accordingly, under *In re Wands*, a determination of enablement is based **not solely on a single factor or a selection of the factors, but on a combination of the factors, taken as a whole.**

When the Wands factors are applied to the claims of the present application, the Applicants maintain that the specification, coupled with the information known in the art, would enable one skilled in the art to use the invention without undue experimentation. The applicants further maintain that each of the factors under *In re Wands* were adequately addressed in the response to the Office Action filed June 3, 2004. However,

[2] *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

in order to provide structure to the Applicant's response, each of the enablement factors is further discussed in detail below.

(a) The Quantity of Experimentation Necessary and the Amount of Direction or Guidance Presented

The Applicants note that the courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP § 2164.01.[3]

In response to the Applicant's arguments filed on June 3, 2004, in the paragraph bridging pages 5 and 6 of the Office Action, the Examiner states the following:

> There is insufficient guidance as to the structure of all "targeting molecules" of the bifunctional molecule that binds to all "intracellular biodistribution modulating protein", and all "drug active derivative thereof" and "small molecule" of the bifunctional molecule for the claimed method without the amino acid sequence, let alone how to make all the molecule for the claimed method...Further, there is insufficient guidance as to which undisclosed "small molecule", and "derivative" of which drug is effective for targeting to which intracellular space when optionally joined by a linking group to any targeting moiety that binds to all intracellular biodistribution modulating protein.

With respect to the targeting moiety, without conceding as to the correctness of the rejection and in the spirit of expediting prosecution, the claims have been amended to recite "said targeting moiety has an affinity for its intracellular protein of at least about 10^{-4} M". Support for the amendment can be found in the claims as originally filed and throughout the specification at, for example, page 20, lines 21-30. As such the claims are not directed to all targeting molecules but specifically, those targeting molecules that (1) when in complex with a drug moiety with or without an optional linker molety, the complex as a whole does not exceed 5000 daltons, and (2) have an affinity for their intracellular protein of at least about 10^{-4} M. Accordingly, such language provides sufficiently functional limitations for the targeting moiety suitable for use in the claimed

[3] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

invention. This limitation serves to distinguish what is claimed from other binding interactions, and furthermore can be coupled with assays which are well known and routine in this field.

In addition, with respect to "derivatives" the Applicants note that the specification provides adequate description to enable one skilled in the art to practice the invention without undue experimentation. For example, beginning on page 8, line 13, the specification provides the following:

> **Specific drugs of interest from which the drug moiety may be derived include**, but are not limited to: psychopharmacological agents, such as (1) central nervous system depressants, e.g. general anesthetics (barbiturates, benzodiazepines, steroids, cyclohexanone derivatives, and miscellaneous agents), sedative-hypnotics (benzodiazepines, barbiturates, piperidinediones and triones, quinazoline derivatives, carbamates, aldehydes and derivatives, amides, acyclic ureides, benzazepines and related drugs, phenothiazines, etc.), central voluntary muscle tone modifying drugs (anticonvulsants, such as hydantoins, barbiturates, oxazolidinediones, succinimides, acylureides, glutarimides, benzodiazepines, secondary and tertiary alcohols, dibenzazepine derivatives, valproic acid and derivatives, GABA analogs, etc.) , analgesics (morphine and derivatives, oripavine derivatives, morphinan derivatives, phenylpiperidines, 2,6-methane-3-benzazocaine derivatives, diphenylpropylamines and isosteres, salicylates, p-aminophenol derivatives, 5-pyrazolone derivatives, arylacetic acid derivatives, fenamates and isosteres, etc.) and antiemetics (anticholinergics, antihistamines, antidopaminergics, etc.), (2) central nervous system stimulants, e.g. analeptics (respiratory stimulants, convulsant stimulants, psychomotor stimulants), narcotic antagonists (morphine derivatives, oripavine derivatives, 2,6-methane-3-benzoxacine derivatives, morphinan derivatives) nootropics, (3) psychopharmacologicals, e.g. anxiolytic sedatives (benzodiazepines, propanediol carbamates) antipsychotics (phenothiazine derivatives, thioxanthine derivatives, other tricyclic compounds, butyrophenone derivatives and isosteres, diphenylbutylamine derivatives, substituted benzamides, arylpiperazine derivatives, indole derivatives, etc.), antidepressants (tricyclic compounds, MAO inhibitors, etc.), (4) respiratory tract drugs, e.g. central antitussives (opium alkaloids and their derivatives)

(emphasis added).

Respectfully, this is a sufficiently comprehensive list of representative examples to support the claimed "derivatives."

In addition, a description of derivatives of pharmacodynamic agents is provided on page 9, lines 6-21, and a description of derivatives of chemotherapeutic agents is provided on page 9, line 22 through page 10, line 11, with descriptions of additional derivatives of other types of drugs provided on page 10, line 12 through page 11, line 11. Accordingly, the specification provides abundant description of "derivatives" suitable for use with the subject invention.

Furthermore, with respect to "small molecule" the Applicants note that the specification specifically provides the following description on page 6, lines 16-23, and page 16, lines 25-30:

> **it generally has a molecular weight of at least about 50 D, usually at least about 100 D, where the molecular weight may be as high as 500 D or higher, but will usually not exceed about 2000 D.**

Accordingly, the specification provides sufficient functional limitations for defining a "small molecule" suitable for use in the claimed invention. In fact, the claims are not directed to any and all "small molecules" per se, but are limited to those which do not exceed 5000 daltons, a specific size that is enabled by the examples.

In view of the above, it is clear that the specification provides sufficient guidance and description for one of skill in the art to make and use the claimed invention without undue experimentation. Though perhaps time-consuming, it is well within the skill of the ordinary practitioner to obtain a drug moiety and a targeting moiety as claimed, and to link them to form a bifunctional molecule (with or without a linker moiety) as taught in the specification, using well known methods of synthetic organic chemistry.

Moreover, the bifunctional molecules which are most suitable for use in the claimed methods can be identified using well known screening techniques described in the specification, with some experimentation, and with a reasonable expectation of success. In this field, a person of ordinary skill in the art would not consider the

experimentation to be undue, because the synthesis and evaluation of large numbers of compounds is expected and routine in the pharmaceutical arts.

As such, the Applicants maintain that sufficient arguments were provided in the response filed June 3, 2004, establishing that the art is not as unpredictable nor the experimentation excessive or undue as is stated by the Examiner. On the contrary, the art recognizes and accepts that although there is some unpredictability, requiring considerable experimentation, the practitioner would not consider this undue, because such a degree of experimentation is routinely practiced, with a reasonable expectation of successful results. It is reasonably predictable that a meaningful number of resulting compositions will be suitable for the intended purpose, even if other compositions are inoperable. Stated another way, the "odds" in this field are acceptable, and so the experimentation that is customary to achieve success is not "undue." Thus, the Applicants maintain that one skilled in the art, with the guidance provided in the specification, could practice the claims of the present invention without undue experimentation.

(b) The Presence or Absence of Working Examples

Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed, nor that examples be "working" examples. No more is needed than that the invention be disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation. Furthermore, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[4] In view of the above described extensive guidance provided by the specification in the present application, it is respectfully submitted that the present application does enable a person skilled in the art to apply the teachings in the specification in conjunction with the relevant art to make and use the full scope of claimed invention.

Furthermore, as previously noted in the response filed on June 3, 2004, specific representative examples are provided. Embodiments of the claimed bifunctional

molecules having a drug moiety bound to FK506 or rapamycin are provided in the Experimental section of the specification, beginning at page 33. In this exemplary embodiment the drug moiety and FK506 or rapamycin targeting moiety are connected by an inert linking group. The resulting bifunctional molecules are suitable for "targeting to the intracellular space" as claimed. Specification, p. 33. Specific drug moieties in the bifunctional molecules, for targeting specific types of cells, are also exemplified. *See*, specification at 33-34 (melanoma, liver, and microbial cells). Targeting moieties which bind to endogenous peptidyl-prolyl isomerase modulating proteins are also exemplified, such as FKBPs and cyclosphilins, as well as FK506, which is further described as a representative targeting moiety. Specification, at 26-28.

The disclosure is not limited to these examples, nor should the claims be so limited. These are representative examples, showing a proof of principle for the concept of the invention, and demonstrating that, generically, the claimed bifunctional molecules are enabled. With this guidance in hand, it would not require undue experimentation to substitute a different drug moiety and if desired an appropriate corresponding targeting moiety. These examples show that the bifunctional compounds can readily be made, and they show that there is a reasonable expectation of success for the full scope of the pairs of drug and targeting moieties claimed.

Moreover, the Applicants note that the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims. Under MPEP § 2164.02 the consideration is whether one skilled in the art would be expected to be able to extrapolate the provided examples across the entire scope of the claim. As presented herein, Applicants argue that it would be reasonable to conclude that one skilled in the art would be able to extrapolate the representative examples provided in the specification across the across the entire scope of the claims without excessive and undue experimentation.

Accordingly, the Applicants maintain that these examples, together with the rest of the specification, and given the knowledge in the art at the time of the invention, are sufficient to provide an enabling disclosure.

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[4] *In re Robins*, 166USPQ 522 (CCPA 1970).

(c) The Nature of the Invention

The invention is in the fields of synthetic organic chemistry, pharmacology and biotechnology. More specifically, the claimed invention is directed to engineered bifunctional molecules for directing a drug to an intracellular space. Therefore, such methods may generally encompass protein biochemistry and small molecule chemistry. As such, the nature of the invention typically involves experimental research that may include manipulation and/or analyzing protein-protein interaction and/or protein-small molecule interaction. Accordingly, the nature of the invention is that practitioners of this art are prepared to perform experimental research. As such, when viewed in light of the ample guidance provided by the specification, the state of the art, the high relative skill of those in the art, etc., the amount of experimentation, if any, needed to practice the subject invention is not excessive.

(d) The State of the Prior Art

As noted above, the invention is in the fields of synthetic organic chemistry, pharmacology and biotechnology. More specifically, the claimed invention is directed to engineered bifunctional molecules for directing a drug to an intracellular space. Accordingly, as noted in detail above the state of the art is sufficiently well developed as evidenced by the numerous publications in the relevant field. As such, the Applicants maintain that the state of the art is well developed such that one skilled in the art would be able to readily address any technical concerns.

(e) The Relative Skill of Those in the Art

There is a high level of skill of those in the art who practice the present invention. Typically, practitioners of the art of protein biochemistry and small-molecule chemistry are highly skilled in fields such as the biological, biochemical, and chemical sciences and the like and typically possess advanced degrees. Accordingly, one skilled in the relevant art would be capable of addressing the technical concerns that the Examiner specifically raised in the Office Action.

(f) The Predictability or Unpredictability in the Art

It is respectfully submitted that the relevant field of the invention is not so unpredictable, as asserted by the Examiner. Specifically, it is submitted that, using the guidance provided in the specification and the knowledge of those of ordinary skill in the art, one could make bifunctional drugs of the multitude of drugs listed on pages 6 to 16 of the specification, by using conventional chemistry linking protocols, such as the representative protocols provided in the specification. Accordingly, it is predictable that one could successfully make bifunctional molecules of the multitude of drugs provided in the specification, e.g., by linking the drugs directly to a targeting moiety or by using a linker disclosed in the specification. It is also predictable that routine testing, including well known screening methods, will successfully identify those bifunctional molecules which target the intracellular space compared to a free drug control. Although experimentation is needed, and all experimentation is somewhat uncertain, the amount of experimentation is ordinary and expected in this field, and *success* is reasonably predictable. See e.g., In re Geerdes, 180 U.S. P.Q. 789 (CCPA, 1974).

(g) The Breadth of the Claims

The Examiner asserts that the breadth of the claims includes the administration of a genus of bifunctional molecules, which is considered unduly large. However, in view of the amendments to the claims, the extensive guidance of the specification, the advanced nature of the field, the high level of skill of those in the art, and the predictability of success in being able to make and use the bifunctional molecules as claimed, it is submitted that the scope of the claims is fully enabled by the specification.

As explained above, a person of ordinary skill in the art, from the specification, would be able to link a known drug to a targeting moiety, including those exemplified in the disclosure, in order to improve bio-distribution to an intracellular space compared to the drug alone, with reasonable experimentation and reasonable expectation of success.

In sum, the amount of experimentation required to subject invention would not be undue and excessive because working examples have been provided, guidance is

given on how to generate such compounds, and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the relevant *Wands* factors.

In view of the above, it is respectfully submitted that Claims 16-18, 22-26, 30-34 and 36 are fully enabled under 35 U.S.C. § 112, 1st ¶ and that this rejection may be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph – Written Description

The Office Action maintains the rejection of Claims 16-18, 22-26, 30-34 and 36 under 35 U.S.C. § 112, 1st ¶ for assertedly failing to comply with the written description requirement. This rejection is respectfully traversed.

In response to the Applicant's arguments filed on June 3, 2004, in the paragraph bridging pages 9 and 10 of the Office Action, the Examiner states "there is inadequate written description about the structure of all 'active drug derivative', and all 'small molecules' optionally linked to all 'targeting molecules'".

However, as noted in detail above, the bifunctional molecules employed in the subject methods are extensively described in the specification beginning at page 4 of the specification. This extensive description includes a generic description of these molecules, a description of these molecules in terms of formulas, an extensive description of each of the component parts of the molecules, e.g., drug moieties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23) as well as a detailed description of how to make these targeted bifunctional molecules (see pages 24 to 28). Furthermore, the specification provides extensive discussion of how to screen bifunctional molecules for desirable activity, and how to use, them for various applications, (including details on dosages, dosage forms and routes of delivery). As such, the bifunctional molecules are fully described in the specification both in terms of component parts, how to make them, and the resulting bifunctional molecules. The bifunctional molecules are described in structural terms, as well as in terms of functional characteristics arising from those structures – particularly

the component parts and how they are linked. One of skill in the art would read the specification and know that the Applicants were in possession of the invention as claimed: a generic method for directing a drug to an intracellular space by linking the drug to a targeting moiety, compared to the drug alone.

With respect to the targeting moiety, without conceding as to the correctness of the rejection and in the spirit of expediting prosecution, the claims have been amended to recite "said targeting moiety has an affinity for its intracellular protein of at least about 10^{-4} M". Support for the amendment can be found in the claims as originally filed and throughout the specification at, for example, page 20, lines 21-30. As such the claims are not directed to all targeting molecules but specifically, those targeting molecules that (1) when in complex with a drug moiety through an optional linker moiety, the complex as a whole does not exceed 5000 daltons, and (2) have an affinity for their intracellular protein of at least about 10^{-4} M.

In addition, with respect to "derivatives" the Applicants note that the specification provides adequate description to enable one skilled in the art to practice the invention without undue experimentation. For example, beginning on page 8, line 13, the specification provides a description of specific drugs of interest which the drug moiety may be derived. In addition, a description of derivatives of pharmacodynamic agents is provided on page 9, lines 6-21, and a description of derivatives of chemotherapeutic agents is provided on page 9, line 22 through page 10, line 11, with descriptions of additional derivatives of other types of drugs provided on page 10, line 12 through page 11, line 11. Accordingly, the specification provides abundant description of "derivatives" suitable for use with the subject invention.

Furthermore, with respect to "small molecule" the Applicants note that specification specifically provides the following description on page 6, lines 16-23, and page 16, lines 25-30:

> **it generally has a molecular weight of at least about 50 D, usually at least about 100 D, where the molecular weight may be as high as 500 D or higher, but will usually not exceed about 2000 D.**

Accordingly, the specification provides sufficient functional limitations for defining a "small molecule" suitable for use in the claimed invention.

Moreover, in the Experimental section, additional representative species are disclosed, including chloroquine-containing bifunctional molecules for targeting drugs to melanoma cells (page 34) and quinacrine-containing bifunctional molecules for targeting liver cells (page 34). Accordingly, additional species are disclosed. The Applicants submit that the representative examples are sufficient in kind and number to support the claims.

In view of the above, it is respectfully submitted that the specification demonstrates that the Applicants were in possession of the claimed invention at the time the application was filed. Accordingly, Claims 16-18, 22-26, 30-34 and 36 comply with the written description requirement of 35 U.S.C. § 112, 1st ¶ and this rejection may be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 16-18 and 22-23 have been rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the invention. In particular, the Office Action notes that the "said mammalian host" in claim 16, line 4 has no antecedent basis in base claim 16, line 3 because line 3 recited "a host", not a mammalian host. In view of the amendment to the claim 16, this objection may be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 16-18, 22-23, 24-26, 30-34, and 36 have been rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Szepeshazi et al. (Anticancer Drugs 8(10):974-987 (1997)) as evident by Nagy et al. (PNAS 93:2464-2469 (1996)), and Nagy et al. (PNAS 93:7269-7273 (1996)). This rejection is respectfully traversed.

The claims of the present application are directed to methods for modulating biodistribution of a drug that binds a protein target **in a host**, such as a mammalian host. However, Szepeshazi et al. fails to teach this element of the pending claims.

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987), cert. denied, 481 U.S. 1052 (1987). See also, Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001 (Fed. Cir. 1991).

Since the cited reference fails to teach each and every element as recited in the pending claims, the cited reference fails to anticipate Claims 16-18, 22-23, 24-26, 30-34, and 36. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

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CONCLUSION

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: December 23, 2004

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